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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/813,432	03/31/2004	Thomas E. Wagner	035879-0182	3800

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
06/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/813,432	WAGNER ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-16 and 18* is/are pending in the application.

4a) Of the above claim(s) *5-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,10-16 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 February 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 2/26/2007 in response to the previous Non-Final Office Action (10/24/2006) is acknowledged and has been entered.

Claims 1-3, 5-16 and 18 are pending.

Claims 5-9 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 1-3, 10-16 and 18 are currently under consideration.

Drawings

The drawings were received on 2/26/2007. These drawings are accepted.

Rejections Withdrawn:

Applicant's arguments, see page 2, filed 2/26/2007, with respect to the rejection of claims 1-4 and 10-17 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement have been fully considered and are persuasive. Thus, the rejection has been withdrawn.

Applicant's arguments, see page 4, filed 2/26/2007, with respect to the rejection or claims 1-3 under 35 U.S.C. 102(b) as being anticipated by Corti (WO 01/61017 A2, 2001, IDS) as evidenced by Yang et al. (J. Exp. Med. 1998; 188: 247-254) have been fully considered and are persuasive. Thus, the rejection has been withdrawn.

Applicant's arguments, see page 5, filed 2/26/2007, with respect to the rejection of claims 10-12 and 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Corti (WO 01/61017, 2001, IDS) in view of Patierno et al. (US 6,288,039, 2001)have been fully considered and are persuasive. Thus, the rejection has been withdrawn.

Rejections Maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1 and 3 **remain** rejected under 35 U.S.C. 103(a) as being unpatentable over Terman (US 6,340,461 B1, Jan. 22, 2002) in view of Ruoslahti et al. (US 6,180,084, 2001, IDS).

Terman teaches a pharmaceutical composition comprising a carrier, a superantigen and an immunotherapeutic antigen (column 15, line 40 to column 16, line 4). With regards to the immunotherapeutic antigen, the patent teaches (column 8, lines 1-12 and column 50, lines 10-14) that the immunotherapeutic antigens include, but are not limited to, galactose-1-3-galactose which elicits an acute-phase hyperimmune response. The patent further teaches (column 50, lines 48-54) that the immunotherapeutic antigen, e.g., galactose-1,3-galactose, can be modified with a monoclonal antibody to generate an antigen-antibody conjugate which specifically targets the cell surface of tumor cells.

Terman does not explicitly teach that the immunotherapeutic antigen can comprises a targeting peptide, wherein the targeting peptide comprises asparagine-glycine-arginine (NGR).

Rouslahti et al. teach tumor homing molecules comprising an NGR peptide motif, as well as NGR peptide conjugates (column 3, lines 1-10). Specifically, Rouslahti et al. teach that the NGR peptide targeted conjugates are advantageous over monoclonal antibody directed targeting because the NGR peptides target the vasculature of tumors, thereby reducing the likelihood that the targeted agent will kill sensitive normal tissues (column 1, liens 60 to column 2, lines 24).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute an NGR targeting peptide for the monoclonal antibody taught by Terman in view of Rouslahti et al. One would have been motivated to do so because Rouslahti et al. teach that the NGR peptide targeted conjugates are advantageous over monoclonal antibody directed targeting because the NGR peptides target the vasculature of tumor, thereby reducing the likelihood that the targeted agent will kill sensitive normal tissues. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering to a patient a pharmaceutical composition comprising a NGR peptide and an immunotherapeutic antigen such as galactose-a-1,3-glalactose, one would achieve a pharmaceutical composition which targets the tumor vasculature and not the tumor cell surface.

In response to this rejection, Applicants assert that the fusion complex of Terman is fundamentally intended to increase the T-cell immune response against the immunotherapeutic antigen to treat cancer and diseases, not to trigger a complement-mediated hyper acute immune reaction as claimed by the present invention. Thus, Applicants assert that the claimed invention utilizes a very different pathway than that of the cited references. Applicants further contend that Terman discloses the use of gal (alpha-3) gal determinants in conjunction with "superantigens... to further promote T cell activation" (col. 50, lines 15-16), wherein this complex may be conjugated to an antibody, as described in the protocol beginning in col. 52, line 17 of Terman. However, Applicants assert that Terman does not disclose a composition comprising a carrier portion, a complement-triggering portion and a targeting portion as claimed. With regards to Ruoslahti, Applicants assert that although Ruoslahti teaches the NGR peptide, the reference does not teach using complement-mediate immune response to kill tumor cells, wherein adding the NGR peptide to the immunotherapy-superantigen complex of Terman would still activate the T-cell mediated immune response. Thus, Applicants assert that the combined references do not teach each and every element of the claims. Moreover, Applicants assert that there would be no expectation of success in achieving the present invention if the teachings of the two references were combined, as neither reference teaches the triggering of complement-mediated immune response. In particular, Applicants contend that while Terman mentions the hyperacute rejection process associated with xenograft rejection (see col. 51, lines 39-55), the reference also teaches the use of an antibody in

conjunction with the carbohydrate-superantigen complex, which destroys the complement reaction, as disclosed in the present application.

These arguments have been carefully considered, but are not found persuasive.

First, in response to applicant's arguments against the references individually, the Examiner recognizes that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references, which make up the state of the art with regard to the claimed invention. Secondly, in response to Applicant's arguments against the combination not using a complement-mediated immune response to kill tumor cells, the Examiner recognizes that the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant, in this case a complement-mediated immune response. *See*, e.g., In re Kahn, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed.Cir. 2006) (motivation question arises in the context of the general problem confronting the inventor rather than the specific problem solved by the invention); Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc., 424 F.3d 1293, 1323, 76 USPQ2d 1662, 1685 (Fed. Cir. 2005). In the instant case, Terman teaches a pharmaceutical composition comprising a carrier, a superantigen and an immunotherapeutic antigen, wherein the immunotherapeutic antigen, e.g., galactose-1,3-galactose, can be modified with a monoclonal antibody to generate an antigen-antibody conjugate which specifically targets the cell surface of tumor cells, whereas Rouslahti et al. teach that the NGR peptide targeted conjugates are advantageous over monoclonal antibody directed targeting because the NGR peptides target the vasculature of tumors, thereby reducing the likelihood that the targeted agent will kill sensitive normal tissues. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering to a patient a pharmaceutical composition comprising a NGR peptide and an immunotherapeutic antigen such as galactose-a-1,3-glalactose, one would achieve a pharmaceutical composition which targets the tumor vasculature and not the tumor cell surface. Furthermore, as admitted by Applicants, "adding the NGR peptide to the immunotherapy-

superantigen complex of Terman would still activate the T-cell mediated immune response". As such, the reasonable expectation of success is high. Thus, for the reasons set forth above, Claims 1 and 3 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Terman (US 6,340,461 B1, Jan. 22, 2002) in view of Ruoslahti et al. (US 6,180,084, 2001, IDS).

Claim 2 **remains** rejected under 35 U.S.C. 103(a) as being unpatentable over Terman (US 6,340,461 B1, Jan. 22, 2002) in view of Ruoslahti et al. (US 6,180,084, 2001, IDS) and in further view of Corti (WO 01/61017, 2001, IDS).

Terman in view of Rouslahti et al. teach, as applied to claims 1 and 3 above, a pharmaceutical composition comprising a carrier an immunotherapeutic antigen and a targeting peptide, wherein the immunotherapeutic antigen is galactose-1,3-galactose and the targeting peptide is a peptide comprising a NGR peptide motif. With regards to the carrier, Terman et al. teach that the carriers include, but are not limited to, serum albumin (column 15, lines 25-31).

Terman in view of Rouslahti et al. do not explicitly teach that the serum albumin carrier is human serum albumin.

Corti teaches a pharmaceutical composition comprising a carrier portion, a targeting portion and an immune response triggering portion, wherein the carrier portion is human serum albumin, the targeting portion is a peptide comprising a NGR motif, and the immune response triggering portion is TNF (page 6, line 27 to page 7, line 7 and page 15, lines1-10). Specifically, Corti teaches that the anti-tumor activity was not changed by the addition of human serum albumin to TNF and NGR-TNF solutions, as the carrier (page 15, lines 1-3)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use human serum albumin as the carrier in the composition taught by Terman and Rouslahti et al. in view of Corti. One would have been motivated to do so because Corti teaches that the anti-tumor activity of TNF was not changed by the addition of human serum as the carrier. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by using human serum albumin as the carrier for a pharmaceutical composition comprising a NGR peptide and an immunotherapeutic antigen such as galactose-a-1,3-glalactose, one would not change the anti-tumor activity of the pharmaceutical composition.

In response to this rejection, Applicants assert that, as discussed above, the composition taught by the combination of Terman and Ruoslahti would elicit a T-cell mediated response, whereas the present invention is directed to compositions eliciting complement-mediated responses. With regards to Corti, Applicants assert that Corti also teaches compositions that trigger a TNF-mediated response. As such, Applicants contend that the combination of cited references does not teach each and every element of the claims and further, a person of skill in the art would have no motivation to combine the references because Corti teaches activation of a pathway that is distinct from those of Terman and Ruoslahti.

These arguments have been carefully considered, but are not found persuasive.

First, Applicants arguments with respect to Terman and Ruoslahti have been fully addressed above and are incorporated herein. Secondly, regarding Applicant's arguments against Corti individually, the Examiner recognizes that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references, which make up the state of the art with regard to the claimed invention. The examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that an "express, written motivation to combine must appear in prior art references before a finding of obviousness." See Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1276, 69 USPQ2d 1686, 1690 (Fed. Cir. 2004). For example, motivation to combine prior art references may exist in the nature of the problem to be solved (Ruiz at 1276, 69 USPQ2d at 1690) or the knowledge of one of ordinary skill in the ad (National Steel Car v. Canadian Pacific Railway Ltd., 357 F.3d 1319, 1338, 69 USPQ2d 1641, 1656 (Fed. Cir. 2004)). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In the instant case, Terman in view of Rouslahti et al. teach a pharmaceutical composition comprising a carrier an immunotherapeutic antigen and a targeting peptide, wherein the immunotherapeutic antigen is galactose-1,3-galactose and the targeting peptide is a peptide comprising a NGR peptide motif,

wherein the carrier includes, but is not limited to, serum albumin, whereas Corti teaches that the anti-tumor activity of NGR-TNF was not changed by the addition of human serum albumin as the carrier. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by using human serum albumin as the carrier for a pharmaceutical composition comprising a NGR peptide and an immunotherapeutic antigen such as galactose-a-1,3-glalactose, one would not change the anti-tumor activity of the pharmaceutical composition. Thus, the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant, in this case a complement-mediated immune response. *See*, e.g., In re Kahn, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed.Cir. 2006) (motivation question arises in the context of the general problem confronting the inventor rather than the specific problem solved by the invention); Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc., 424 F.3d 1293, 1323, 76 USPQ2d 1662, 1685 (Fed. Cir. 2005).

Claims 10-16 **remain** rejected under 35 U.S.C. 103(a) as being unpatentable over Terman (US 6,340,461 B1, Jan. 22, 2002) in view of Ruoslahti et al. (US 6,180,084, 2001, IDS) and in further view of Patierno et al. (US 6,288,039).

Terman in view of Rouslahti et al. teach, as applied to claims 1 and 3 above, a pharmaceutical composition comprising a carrier an immunotherapeutic antigen and a targeting peptide, wherein the immunotherapeutic antigen is galactose-1,3-galactose and the targeting peptide is a peptide comprising a NGR peptide motif. With regards to the NGR peptide motif, Rouslahti et al. teach that the NGR peptide motif specifically homes in vivo to breast tumor, melanoma, as well as, Kaposi's sarcoma (column 17, line 65 to column 18, line 2). In addition to the NGR peptides, Rouslahti et al. teach that aminopeptidase inhibitors such as bestatin can be used for directing a moiety to the angiogenic vasculature of a tumor (column 3, lines 5-10).

Terman in view of Rouslahti et al. do not explicitly teach a kit comprising, in a suitable container, a pharmaceutical composition comprising a carrier portion, a targeting portion and an immune response triggering portion.

Patierno et al. teach pharmaceutical compositions and kits for treating and diagnosing breast cancer (abstract). Specifically, the reference teaches a kit for treating breast cancer comprising a

therapeutically effective amount of an inhibitor in a pharmaceutically acceptable carrier and a device for delivering the inhibitor to the breast cancer, wherein the carrier and device are packaged in a container (column 7, liens 61-67).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to package the pharmaceutical composition as taught by Terman and Rouslahti et al. as a kit in view of the Patierno et al.. One would have been motivated to do so because standard kits enhance the probability of the reproducibility and efficiency of the treatment process and further provide for increased marketability, convenience, reliability, and economy. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by packaging the pharmaceutical composition taught by Terman and Rouslahti et al. as a kit, one would achieve a convenient and reliable kit which can be used for the treatment of breast cancer.

In response to this rejection, Applicants assert that, as discussed above, the composition taught by the combination of Terman and Ruoslahti would elicit a T-cell mediated response, whereas the present invention is directed to compositions eliciting complement-mediated responses. With regards to Patierno, Applicants assert that Patierno merely discloses kits and does not teach compositions that trigger a complement mediated immune response. As such, Applicants contend that the combination of cited references does not teach each and every element of the claims and further, a person of skill in the art would have no motivation or expectation of success for such a combination to arrive at the present invention.

These arguments have been carefully considered, but are not found persuasive.

First, Applicants arguments with respect to Terman and Ruoslahti have been fully addressed above and are incorporated herein. Secondly, regarding Applicant's arguments against Patiero individually, the Examiner recognizes that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references, which make up the state of the art with regard to the claimed invention. The examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and

secondary references In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that an "express, written motivation to combine must appear in prior art references before a finding of obviousness." See Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1276, 69 USPQ2d 1686, 1690 (Fed. Cir. 2004). For example, motivation to combine prior art references may exist in the nature of the problem to be solved (Ruiz at 1276, 69 USPQ2d at 1690) or the knowledge of one of ordinary skill in the ad (National Steel Car v. Canadian Pacific Railway Ltd., 357 F.3d 1319, 1338, 69 USPQ2d 1641, 1656 (Fed. Cir. 2004)). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In the instant case, Terman in view of Rouslahti et al. teacha pharmaceutical composition comprising a carrier an immunotherapeutic antigen and a targeting peptide, wherein the immunotherapeutic antigen is galactose-1,3-galactose and the targeting peptide is a peptide comprising a NGR peptide motif, wherein the carrier includes, but is not limited to, serum albumin, whereas Patierno et al. teach a kit for treating breast cancer comprising a therapeutically effective amount of an inhibitor in a pharmaceutically acceptable carrier and a device for delivering the inhibitor to the breast cancer, wherein the carrier and device are packaged in a container. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by packaging the pharmaceutical composition taught by Terman and Rouslahti et al. as a kit, one would achieve a convenient and reliable kit which can be used for the treatment of breast cancer. Thus, the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant, in this case a complement-mediated immune response. *See*, e.g., In re Kahn, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed.Cir. 2006) (motivation question arises in the context of the general problem confronting the inventor rather than the specific problem solved by the invention); Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc., 424 F.3d 1293, 1323, 76 USPQ2d 1662, 1685 (Fed. Cir. 2005).

Claim 18 **remains** rejected under 35 U.S.C. 103(a) as being unpatentable over Terman (US 6,340,461 B1, Jan. 22, 2002) in view of Ruoslahti et al. (US 6,180,084, 2001, IDS) and Patierno et al. (US 6,288,039) and in further view of Corti (WO 01/61017, 2001, IDS).

Terman in view of Rouslahti et al. and Patierno et al. teach, as applied to claims 10-16 above, a kit in a suitable container comprising a pharmaceutical composition comprising a carrier an immunotherapeutic antigen and a targeting peptide, wherein the immunotherapeutic antigen is galactose-1,3-galactose and the targeting peptide is a peptide comprising a NGR peptide motif. With regards to the carrier, Terman et al. teach that the carriers include, but are not limited to, serum albumin (column 15, lines 25-31).

Terman in view of Rouslahti et al. and Patierno et al. do not explicitly teach that the kit comprises human serum albumin as the carrier.

Corti teaches a pharmaceutical composition comprising a carrier portion, a targeting portion and an immune response triggering portion, wherein the carrier portion is human serum albumin, the targeting portion is a peptide comprising a NGR motif, and the immune response triggering portion is TNF (page 6, line 27 to page 7, line 7 and page 15, lines1-10). Specifically, Corti teaches that the anti-tumor activity was not changed by the addition of human serum albumin to TNF and NGR-TNF solutions, as the carrier (page 15, lines 1-3)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use human serum albumin as the carrier in the kit taught by Terman, Rouslahti et al. and Patierno et al. in view of Corti. One would have been motivated to do so because Corti teaches that the anti-tumor activity of TNF was not changed by the addition of human serum albumin as the carrier. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by using human serum albumin as the carrier for a pharmaceutical composition comprising a NGR peptide and an immunotherapeutic antigen such as galactose-a-1,3-glalactose, one would not change the anti-tumor activity of the pharmaceutical composition.

In response to this rejection, Applicants assert that, as discussed above, the composition taught by the combination of Terman and Ruoslahti would elicit a T-cell mediated response, whereas the present invention is directed to compositions eliciting complement-mediated responses. With regards to Corti and Patierno, Applicants assert that Corti also teaches compositions that trigger a TNF-mediated response and Patierno merely discloses a kit. As such, Applicants contend that the combination of cited references does not teach each and every element of the claims and further, a person of skill in the art would have no motivation or expectation of success for such a combination to arrive at the present invention.

These arguments have been carefully considered, but are not found persuasive.

First, Applicants arguments with respect to Terman and Ruoslahti have been fully addressed above and are incorporated herein. Secondly, regarding Applicant's arguments against Corti and Patierno individually, the Examiner recognizes that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references, which make up the state of the art with regard to the claimed invention. The examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that an "express, written motivation to combine must appear in prior art references before a finding of obviousness." See Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1276, 69 USPQ2d 1686, 1690 (Fed. Cir. 2004). For example, motivation to combine prior art references may exist in the nature of the problem to be solved (Ruiz at 1276, 69 USPQ2d at 1690) or the knowledge of one of ordinary skill in the ad (National Steel Car v. Canadian Pacific Railway Ltd., 357 F.3d 1319, 1338, 69 USPQ2d 1641, 1656 (Fed. Cir. 2004)). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In the instant case, Terman in view of Rouslahti et al. teach a pharmaceutical composition comprising a carrier an immunotherapeutic antigen and a targeting peptide, wherein the immunotherapeutic antigen is galactose-1,3-galactose and the targeting peptide is a peptide comprising a NGR peptide motif, wherein the carrier includes, but is not limited to, serum albumin, whereas Corti teaches that the anti-tumor activity of NGR-TNF was not changed by the addition of human serum albumin as the carrier and Patierno et al. teach a kit for treating breast cancer comprising a therapeutically effective amount of an inhibitor in a pharmaceutically acceptable carrier and a device for delivering the inhibitor to the breast cancer, wherein the carrier and device are packaged in a container. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by using human serum albumin as the carrier for a pharmaceutical composition comprising a NGR peptide and an immunotherapeutic antigen such as galactose-a-1,3-glalactose,

one would not change the anti-tumor activity of the pharmaceutical composition. Thus, the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant, in this case a complement-mediated immune response. *See*, e.g., In re Kahn, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed.Cir. 2006) (motivation question arises in the context of the general problem confronting the inventor rather than the specific problem solved by the invention); Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc., 424 F.3d 1293, 1323, 76 USPQ2d 1662, 1685 (Fed. Cir. 2005).

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Conclusion

Therefore, No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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